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Published

With international search report.

(54) Title: CONTROLLED RELEASE ORAL DELIVERY SYSTEM CONTAINING OXYBUTYNIN

(57) Abstract

The present invention concerns a controlled release drug delivery system for oxybutynin, its manufacture and use. The drug delivery system comprises oxybutynin in combination with a controlled release excipient comprising about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of 1:3 to 3:1, a cationic crosslinking agent for the said hydrophilic material, in an amount of 1 to 20 % by weight, and 20-79 % by weight of an inert filler.

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GA	Gabon				

Controlled release oral delivery system containing oxybutynin.

The present invention relates to controlled or extended release delivery systems for the treatment of disorders responsive to the action of an antispasmodically active agents, especially for the treatment of a neurogenic bladder, a method of preparation of the delivery systems as well as method of using them.

Oxybutynin and its salts, in particular the hydrochloride (hereinafter oxybutynin) is a musculotropic antispasmodic drug with moderate anticholinergic, systemic analgesic and local anaesthetic action. Its relaxant effect on smooth muscle is based on antagonism of a process distal to the neuromuscular junction (papaverine-like effect) and on anticholinergic action on the blockage of muscarine-type receptors. Oxybutynin chloride has been in clinical use for twenty years and it is indicated for the relief of symptoms associated with voiding in patients with an uninhibited neurogenic and reflex neurogenic bladder. It is also used to suppress gastric acid secretion, to relieve post-transurethral vesical pain and spasm in the gastrointestinal tract, to control detrusor dysfunction and to facilitate catheterization of the urinary bladder in myelomeningocele patients. The drug is effective when given orally.

Chemically, oxybutynin hydrochloride (DL-racemic form of 4-diethylamino-2-butynyl-phenyl-cyclohexylglycolate hydrochloride) is a tertiary amine. It is rapidly absorbed from the gastrointestinal tract following oral administration and its pharmacological action starts within one hour. The duration of action of the drug is three to six hours.

It has been established that after the administration of oxybutynin hydrochloride (5 mg dose tablet), the maximum concentration of unmetabolized oxybutynin in plasma was

reached within 1 h, and the elimination half-life was about 2.5 h. Due to the relatively rapid elimination of the active agent from the blood, conventional treatment with oxybutynin has comprised administering oxybutynin in a dose of 5 mg (calculated as the hydrochloride) twice or three times daily, the recommended maximal dose of oxybutynin being 20 mg per day.

In conventional treatment, the administration of oxybutynin is accompanied by a high initial peak concentration in the blood with associated side effects. Furthermore, the frequent need to administer the drug in order to maintain or restore the necessary concentration of active agent in the blood is cumbersome and consequently has a tendency to reduce patient compliance.

Consequently, there is a need for an oxybutynin preparation with a sustained action. Especially there is a need for a preparation which allows for a reduction of the peak initial drug concentration in the blood and which provides for an even and substantially extended effect. Such a preparation would readily allow for a once-a-day treatment with a single oral dose.

According to the invention the afore mentioned aim has been reached by combining oxybutynin or a pharmaceutically acceptable salt thereof, with an excipient allowing the controlled and extended, even release of the active agent over a period of time exceeding 24 hours while simultaneously reducing the initial peak concentrations of active agent in the blood of the patient.

Thus the invention provides a controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising

- a therapeutically effective amount of oxybutynin,

or a pharmaceutically acceptable salt thereof,

- a controlled release excipient comprising
  - about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
  - a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
  - about 20 - 79 % by weight of an inert filler,

the ratio of oxybutynin to hydrophilic material being from about 1:2 to 1:25.

The excipient used in the composition according to the invention thus comprises as one component a hydrophilic material or gelling system comprising on the hand a heteropolysaccharide, and on the other hand a homopolysaccharide which is capable of crosslinking the heteropolysaccharide in an aqueous fluid, such as in a gastric fluid, the ratio between the two types of saccharides being from about 3:1 to 1:3.

The heteropolysaccharide is a water soluble saccharide containing two or more kinds of sugar units, and it has excellent swelling properties. According to a preferred embodiment it comprises a xanthan gum, or a derivative thereof. Such derivatives are deacylated xanthan gum, the carboxymethyl ether and propylene glycol ester.

In the preferred embodiment, the homopolysaccharide comprises one or more galactomannans, and especially galactomannas with a higher ratio of mannose to galactose, e.g. locust bean gum. Other polysaccharides are e.g. guar gum and hydroxypropyl guar gum.

The ratio between heteropolysaccharide and homopolysaccharide is preferably approximately 1:1.

In addition the excipient contains an inert filler or diluent, which suitably is a monosaccharide, disaccharide or polyhydric alcohol, such as sucrose, dextrose, lactose, fructose, xylitol, sorbitol, and microcrystalline cellulose, or mixtures thereof.

The excipient used in the composition according to the invention contains in addition a cationic crosslinking agent which is capable of crosslinking the hydrophilic material, when this is exposed to gastrointestinal fluids, thus strengthening the gel structure and preventing an initial burst of the drug when exposed to a gastrointestinal environment. The amount of cationic crosslinking is at the most about 20 % by weight, such as from bout 1 to 20, especially about 5 to 15 % by weight.

The cationic crosslinking agent can be a mono- or multivalent salt, preferably an inorganic salt such as alkali and/or alkaline earth metal salt, such as sodium, potassium, litium, calcium, magnesium chloride, bromide, sulfate, borate, citrate, acetate, lactate, carbonate, bicarbonate. The cationic crosslinking agent is preferably divalent, such as in calcium sulfate, or it is sodium chloride.

Controlled release excipients containing a combination of hetero- and homopolysaccharides as defined above with inert diluents, have been described in the US patents 4,994,276, 5,128,143, and 4,135,757.

In a preferred embodiment the excipient contains about 25 to 50, especially about 25 to 35 % by weight of the hydrophilic material or gelling system, about 5 to 15 % by weight of cationic crosslinking agents, and about 35 to 70, especially about 50 to 70 % by weight of inert diluent.

The ratio of oxybutynin (calculated as its hydrochloride) to hydrophilic material is preferably about 1:5 to 1:15. A suitable amount of oxybutynin in a single dose, such as in a tablet, is about 5 to 20 mg, especially about 10 mg. A suitable daily dose of opxybutynin is from about 0.05 to 0.25 mg/kg body weight, especially appr. 0.12 mg/kg body weight.

The drug delivery system according to the invention can be made by first dry blending the ingredients for the excipient, and then granulating the mixture in the presence of small amount of fluid, such as water. The obtained granulate is therafter combined with the active ingredient for example by simple dry-blending, or by using wet granulation techniques, using e.g. water as the granulating fluid.

According to an embodiment of the invention, a suitable lubricant, known per se, can be added to the excipient and drug components to be combined. The choice of lubricants is well known in the art, and magnesium, calcium and sodium stearate may be mentioned. A suitable amount of lubricant is appr. 0,5 to 3 % by weight.

The drug-excipient mixture prepared may be compressed to tablets according to conventional tablet formation techniques. The blend may also be used as pellets, as a granulate or powder, or filled in capsules. The dosage formed obtained may be coated using any suitable coating system. Such coating systems and coating techniques are well known in the art.

According to the invention it is possible to add to the composition further agents and additives, e.g. hydrophobic agents for regulating the hydration of the product, for example by including polymeric cellulose derivatives, such as alkyl celluloses, polymeric acrylic and methacry-

lic acid derivatives, waxes, oils etc. usually in amounts amounting to about 1 to 20 % by weight. Such an addition replaces part of the inert diluent. The hydrophobic agents are as such well known in the art, and a number of them are commercially available. It is also possible to add release rate decreasing substances to the mixture of drug and excipient, for example microcrystalline cellulose in an amount of about 1 to 10 % by weight.

The present invention also concerns a method for treating a subject of a condition responsive to the action of an antispasmodically active agent, such as voiding resulting from uninhibited or reflex neurogenic bladder, gastric acid secretion, vesical pain, gastrointestinal tract spasm and detruson dysfunction, especially of neurogenic bladder, the method comprising administering to the subject for oral ingestion a delivery system, especially a tablet, according to the invention as defined above.

The invention also concerns a method of maintaining, in a human subject, a therapeutically sufficient blood level concentration of oxybutynin or of an active metabolite thereof, such as N-desethyl oxybutynin, for an extended period of time, the method comprising administering orally to the said subject a controlled release delivery system according to the invention, as defined above, especially a tablet containing 5 to 20 mg of oxybutynin. Preferably a therapeutically sufficient blood level concentration is maintained for at least about 24 hours after administration of a single dose of oxybutynin, such as a single dose of about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight, of oxybutynin or a salt thereof, e.g. the hydrochloride. The administration of a daily single dose of a 10 mg controlled release oxybutynin tablet gave blood level concentrations of oxybutynin of at least about 0.5 ng/ml, such as 0.5 to 2.0 ng/ml for a period of at least about 24 hours, the value following

the peak value being in the area of about 0.5 to 1.0 ng/ml, as is evident from the test report.

The following examples illustrate the invention, however, without limiting the scope thereof. Parts and percentages are by weight, unless otherwise stated.

Examples 1 - 2:

In Examples 1-2, controlled release excipients in accordance with the present invention were first prepared, the oxybutynin being added subsequently, and the final mixture then being tableted.

The excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, calcium sulfate, and dextrose in a high speed mixer/granulater for 2 minutes. While running choppers/impellers, the requisite amount of water was added to the dry blended mixture, and granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a LOD (loss on drying) of less than about 10% by weight (e.g. 4-7% LOD). The granulation was then milled using 20 mesh screens. The ingredients of the granulations of Examples 1-2 are set forth in Table 1 below:

TABLE 1

Preparation of sustained-release excipient

Component	% - Ex. 1	% - Ex. 2
1. Xanthan Gum	25	25
2. Locust Bean Gum	25	25
3. Dextrose	40	30
4. Calcium Sulfate	10	20
5. Water	10*	10*

*Removed during processing.

Next, the excipient prepared as detailed above was dry blended with the desired amount of oxybutynin HCl in a V-blender for 10 minutes. A suitable tableting lubricant (Pruv®, sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc) was added, and the mixture was blended for another 5 minutes. This final mixture was compressed into tablets. The ingredients of the tablets of Examples 1-2 are set forth in Table 2 below:

TABLE 2

Tablet formulation - Examples 1-2

Component	% - Ex. 1	% - Ex. 2
1. Excipient	93.8	93.8
2. Oxybutynin HCl	4.7	4.7
3. Sodium stearyl fumarate	1.5	1.5
Tablet weight (mg)	213.2	213.2
Hardness (Kp)	3.3	1.4

Examples 3-4:

In Examples 3-4, a controlled release excipient was prepared in accordance with the procedures set forth for Examples 1-2. The ingredients of the sustained release matrix of Examples 3-4 are set forth in Table 3 below:

TABLE 3

Component	% - Ex. 3	% - Ex. 4
1. Xanthan Gum	15	15
2. Locust bean Gum	15	15
3. Dextrose	60	60
4. Calcium Sulfate	10	10
5. Water	10*	10*

*Revomed during prosessing.

Thereafter, oxybutynin tablets were prepared in accordance with the procedure set forth in Examples 1-2. The ingredients of the tablets of Examples 3-4 are set forth in Table 4 below:

TABLE 4

Component	% - Ex. 3	% - Ex. 4
1. Excipient	95.7	93.0
2. Oxybutynin HCl	2.9	5.6
3. Sodium stearyl fumarate	1.4	1.4
Tablet weight (mg)	348.3	179.3
Hardness (Kp)	10.4	3.3

In Example 3, the drug:gel ratio is about 1:10. In Example 4, the drug:gel ratio is about 1:5. By "gel" it is meant the combined weight of xanthan gum and locust bean gum.

TEST REPORT

A bioequivalence study was carried out to assess the bioavailability of oxybutynin from a delivery system according to the invention, using as a reference system an ordinary 5 mg oxybutynin chloride containing tablet, after a single peroral dose of 10 mg of oxybutynin chloride.

The study was performed as a balanced, randomized, three-period cross-over study on 24 healthy volunteers.

Pharmacokinetics

From serum concentrations of oxybutynin and its metabolite N-desethyl oxybutynin the following pharmacokinetic parameters were calculated:

- AUC_{0-t} using the linear trapezoidal rule (t was the last detectable concentration).
- C_{max} and t_{max} were used as measured

The individual and mean serum time-concentration curves for both oxybutynin and its metabolite N-desethyl oxybutynin were provided.

The pharmacokinetic parameters were calculated and curves created using the Siphar program.

Fourteen (14) blood samples (10 ml each) were taken during each study period according to the following schedule: 0 (pre-drug), 0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hours following drug administration. A total of 420 ml blood was taken over the three study phases, exclusive of pre- and post-clinical blood work (30 ml).

All urine excreted during 24 h after administration of the drug was collected as follows: one sample was taken before administration (blank sample); thereafter, samples in fractions of four hours up to 12.0 h after administration (0.0-4.0 h, 4.0-8.0 h and 8.0-12.0 h), and in a fraction of twelve hours up to 24.0 h (12.0-24.0 h).

Urine fractions were measured by volume, and aliquots of 2-3 ml separated into duplicate polypropylene tubes, frozen immediately and stored at -20°C for later examination.

Evaluations

The data from this study was analyzed by comparing the pharmacokinetic parameters calculated for the controlled release tablet (test preparation) to those for the ordinary tablet (reference preparation).

Analytical methods

Analysis of oxybutynin and its metabolite N-desethyl oxybutynin in serum were carried out by a capillary gas chromatographic method using mass selective detector. The quantification limit of the method was 0.2 ng/ml for unchanged oxybutynin and 2.5 ng/ml for the metabolite. The method is linear from 0.2 ng/ml to 30 ng/ml for oxybutynin and from 2.5 to 150 ng/ml for N-desethyl oxybutynin, respectively.

Results

There were no statistically significant differences in the extent of oxybutynin in serum after administration of the controlled release tablet (Md AUC_{0-t}= 17.02 ng/ml*h) compared to that after intake of two 5 mg ordinary tablets (the reference preparation, Md AUC_{0-t}= 15.86 ng/ml*h).

The peak serum concentration of oxybutynin after the test controlled release tablet (Md C_{max}= 2.13 ng/ml) was however significantly lower and it was reached significantly later (Md t_{max}= 1.5 h) than those after administration of the reference tablets (Md C_{max}= 6.86 ng/ml, Md t_{max}= 0.75 h). This is also shown in the appended Figures 1 and 2. In these Figures, Fig. 1 shows the mean serum concentration of oxybutynin as a function of time after administartion of a 10 mg controlled release tablet of the invention, and 2 * 5 mg conventional tablets. Fig. 2 shows the serum concentration of the metabolite, N-desethyl oxybutynin after the said administration.

The clinical importance of the extended release pattern of the controlled release tablet was demonstrated by statistically significantly less anticholinergic side-effects compared to the conventional tablet. Furthermore, the high and persistent levels of the active metabolite of oxybutynin for the whole 24 h study period reflects the extended release characteristics of the 10 mg controlled release tablet.

In summary,

1. The controlled release tablet of the invention gave a reliable pharmacokinetic profile of an extended release formulation covering the 24-hour study period.

2. There were no statistically significant differences in the AUC of oxybutynin in serum after administration of the test controlled release tablet compared to that after intake of two 5 mg ordinary tablets.

3. The controlled release tablet can be considered a successful and clinically bioequivalent formulation when lower peak concentrations of oxybutynin in serum are desirable to diminish anticholinergic side-effects of oxybutynin.

Claims:

1. A controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising

- a therapeutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
  - about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
  - a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
  - about 20 - 79 % by weight of an inert filler,

the ratio of oxybutynin to hydrophilic material being from about 1:2 to 1:25.

2. The delivery system according to claim 1, wherein the the ratio of oxybutynin to hydrophilic material is about 1:5 to 1:15.

3. The delivery system according to claim 1 wherein the oxybutynin is in the form of its hydrochloride salt.

4. The delivery system according to claim 3 in the form of a tablet containing from 5 to 20 mg of oxybutynin hydrochloride.

5. The delivery system according to claim 3 in the form of a tablet containing about 10 mg of oxybutynin hydrochloride.

6. A method of making a controlled release oral delivery system for the treatment of disorders responsive to the action of an antispasmodically active agent, comprising providing a controlled release excipient by combining

- about 15 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1, with

- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight, and with

- about 20 - 79 % by weight of an inert filler,

combining said obtained controlled release excipient with oxybutynin, or a pharmaceutically acceptable salt thereof in an amount as to provide a ratio of oxybutynin to hydrophilic material from about 1:2 to 1:25, and, optionally using pharmaceutically acceptable adjuvants, forming the obtained mixture into a solid dosage form.

7. The method according to claim 6, wherein oxybutinin is used as its hydrochloride salt, the ratio of oxybutynin to hydrophilic material being about 1:5 to 1:15.

8. The method according to claim 7 wherein the mixture is compressed into tablets each containing from 5 to 20 mg, advantageously about 10 mg of oxybutynin hydrochloride.

9. Use of oxybutynin or its pharmaceutically acceptable salt for the preparation of an oral drug delivery system according to claim 1, providing extended and even release of the active agent over a period of time of at least 24 hours, for the treatment of disorders responsive to the effect of an antispasmodically active agent.

10. Use oxybutynin or its salt according to claim 9 for the preparation of a drug delivery system for the treatment of a neurogenic bladder.

11. A method for treating a subject for relief of a condition responsive to the action of an antispasmodically active agent, the method comprising administering to the subject for oral ingestion a delivery system comprising:

- a pharmaceutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
- about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
- about 20 - 79 % by weight of an inert filler, the ratio of oxybutynin to hydrophilic material being from about 1:2 to about 1:25.

12. The method according to claim 11 wherein the condition to be treated is selected from the group consisting of voiding resulting from uninhibited or reflex neurogenic bladder, gastric acid secretion, vesical pain, gastrointestinal tract spasm and detruson dysfunction.

13. The method according to claim 12, wherein the condition to be treated is neurogenic bladder.

14. The method according to claim 11, wherein the delivery system is a tablet containing from about 5 to 20 mg of oxybutynin hydrochloride.

15. The method according to claim 11 wherein oxybutynin hydrochloride is adminstered once-a-day in a single dose containing about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight of oxybutynin hydrochloride.

16. A method for maintaining a therapeutically sufficiently high blood level concentration of oxybutynin or of an active metabolite thereof, in a human subject, for an extended period of time, the method comprising administering orally to the subject a delivery system comprising:

- a pharmaceutically effective amount of oxybutynin, or a pharmaceutically acceptable salt thereof,
- a controlled release excipient comprising
- about 20 to 60 % by weight of a hydrophilic material comprising a heteropolysaccharide and a homopolysaccharide, in a ratio of about 1:3 to 3:1,
- a cationic crosslinking agent for the said hydrophilic material, in an amount of about 1 to 20 % by weight,
- about 20 - 79 % by weight of an inert filler, the ratio of oxybutynin to hydrophilic material being from about 1:2 to about 1:25.

17. The method according to claim 16 wherein the extended period of time is at least about 24 hours.

18. The method according to claim 16 or 17 wherein oxybutynin hydrochloride ia administered once-a-day in a single dose containing about 0.05 mg/kg to 0.25 mg/kg, especially about 0.12 mg/kg body weight of oxybutynin hydrochloride.

FIG. 1

THE MEAN CONC. OF OXYBUTYNIN

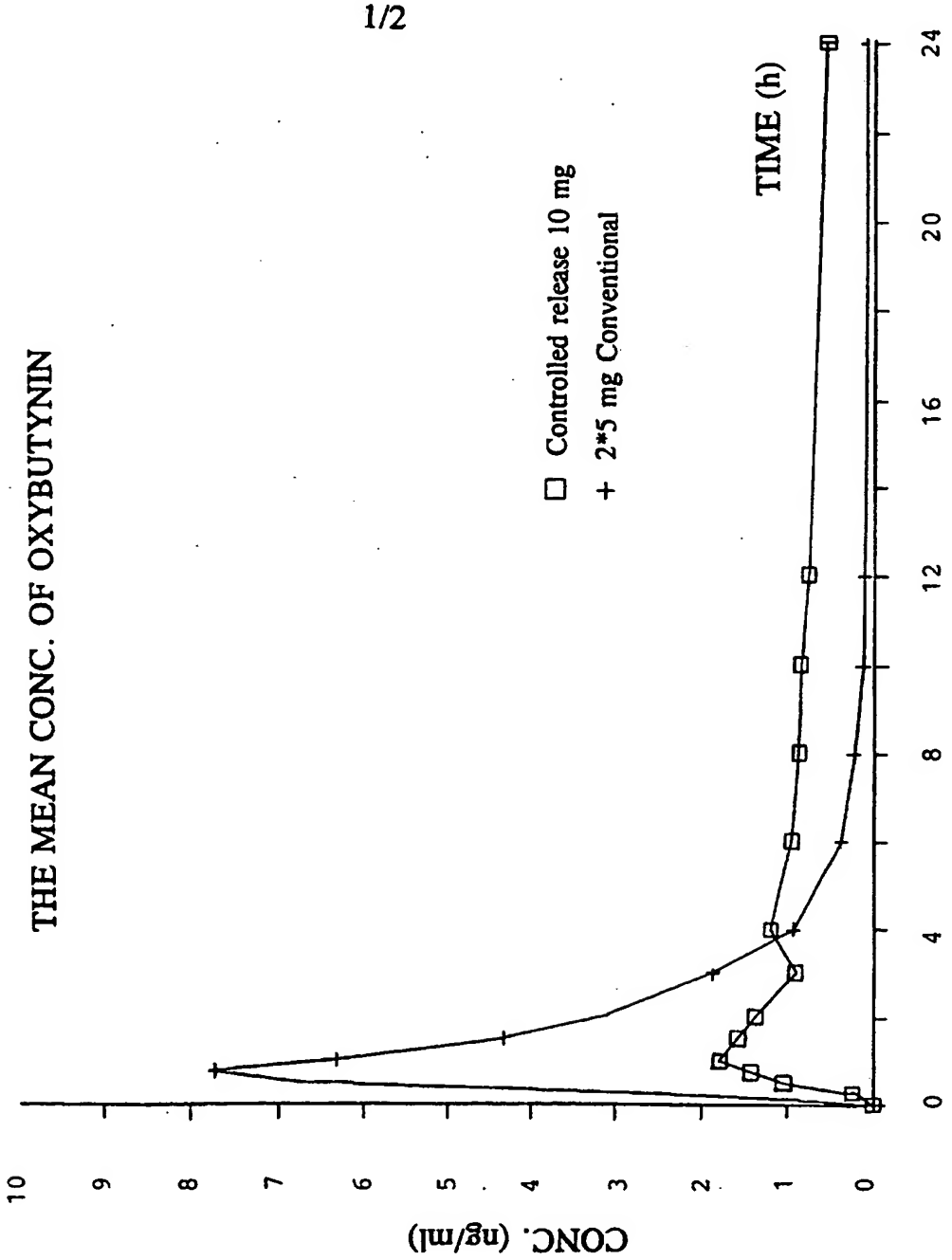
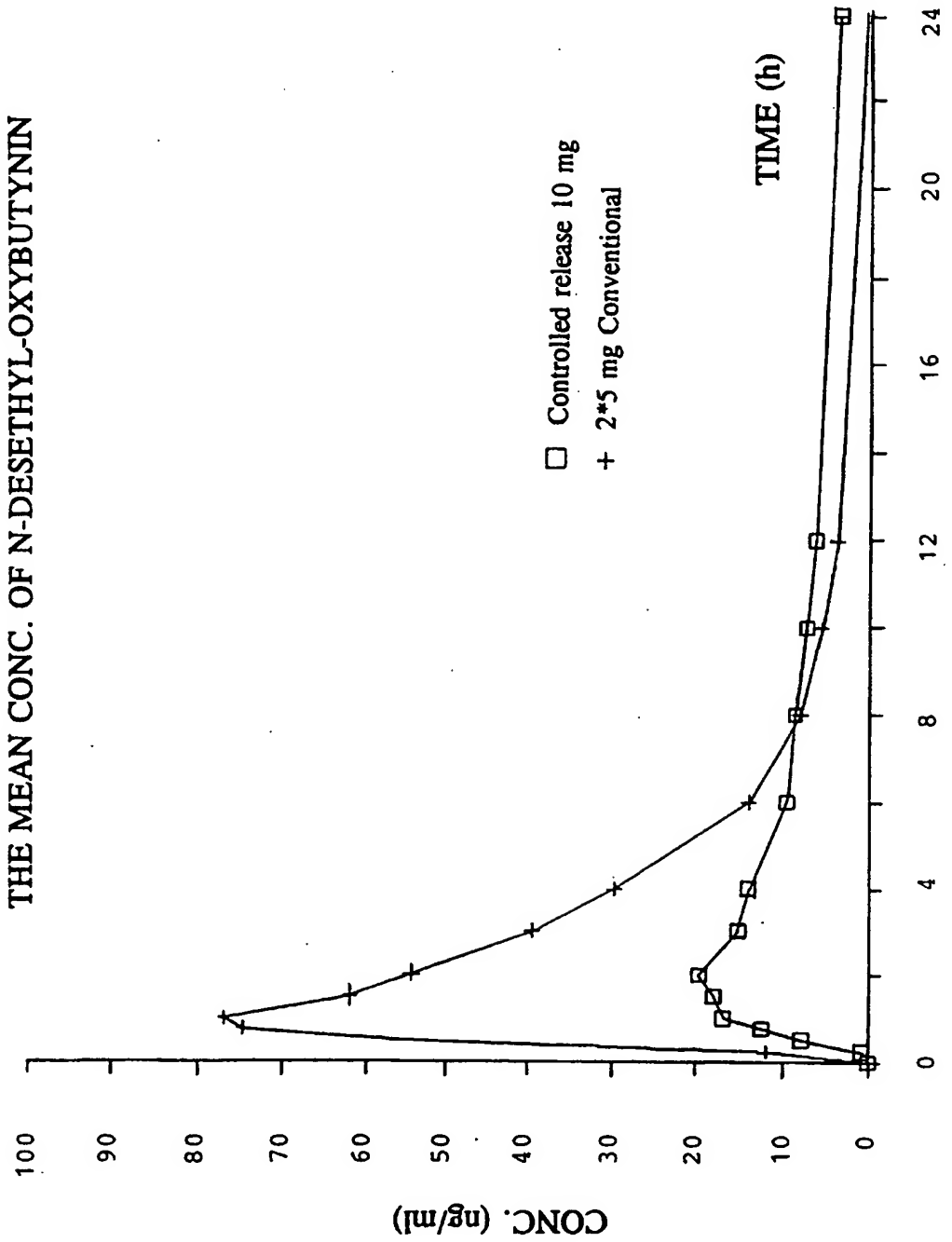


FIG.2


THE MEAN CONC. OF N-DESETHYL-OXYBUTYNIN
Controlled release 10 mg
2*5 mg Conventional
TIME (h)
CONC. (ng/ml)
0
10
20
30
40
50
60
70
80
90
100
0
4
8
12
16
20
24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/22, A61K 31/215
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US, A, 5399359 (ANAND R. BAICHWAL), 21 March 1995 (21.03.95) --	1-10
X	US, A, 5169639 (ANAND R. BAICHWAL ET AL), 8 December 1992 (08.12.92), claims --	1-10
X	US, A, 5135757 (ANAND R. BAICHWAL ET AL), 4 August 1992 (04.08.92), column 6, line 49 - column 10, line 9, claims --	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1995	13 -06- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0497977 (NIPPON SHINYAKU CO., LTD.), 12 August 1992 (12.08.92), column 7, line 22 - line 27, examples 4-6	1-10

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 94/00474

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-18
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/05/95

International application No.
PCT/FI 94/00474

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5399359	21/03/95	NONE	
US-A- 5169639	08/12/92	AU-B- 623182	07/05/92
		AU-A- 4305789	18/04/90
		DE-T- 68907835	11/11/93
		EP-A,A,A 0360562	28/03/90
		SE-T3- 0360562	
		ES-T- 2059778	16/11/94
		JP-T- 4501713	26/03/92
		JP-B- 6025073	06/04/94
		US-A- 4994276	19/02/91
		US-A- 5128143	07/07/92
		US-A- 5135757	04/08/92
		US-A- 5171440	15/12/92
		WO-A- 9003165	05/04/90
		AU-B- 649163	12/05/94
		AU-A- 2403392	23/02/93
		CA-A- 2092287	26/01/93
		EP-A,A- 0550737	14/07/93
		HU-A- 64221	28/12/93
		JP-T- 6500576	20/01/94
		WO-A- 9301803	04/02/93
US-A- 5135757	04/08/92	AU-B- 623182	07/05/92
		AU-A- 4305789	18/04/90
		DE-T- 68907835	11/11/93
		EP-A,A,A 0360562	28/03/90
		SE-T3- 0360562	
		ES-T- 2059778	16/11/94
		JP-T- 4501713	26/03/92
		JP-B- 6025073	06/04/94
		US-A- 4994276	19/02/91
		US-A- 5128143	07/07/92
		US-A- 5169639	08/12/92
		US-A- 5171440	15/12/92
		WO-A- 9003165	05/04/90
EP-A1- 0497977	12/08/92	DE-D- 69017915	00/00/00
		US-A- 5368861	29/11/94
		AT-T- 119766	15/04/95
		WO-A- 9106281	16/05/91